Academic and Clinical Central Office for Research and Development

Clinical Investigation Plan

Pneumonia Investigation Bundle to Guide Therapy for Hospitalised Community Acquired Pneumonia (PIB CAP Study)

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3.0	12 Mar 19	• Removed list of participating sites • Added document history section • Updated section 4.4 with the latest ACCORD co-enrolment policy • Updated section 6.1.3 with more information about timing of QA/QC, and release, receipt and access to the PIBCAP assay reagents • Removed CHI/NHS number collection and potential data linkage, sections 7.3 and 9.1 updated
4.0	05 Jul 19	• ISRCTN registration added • Clarification to table 1 (section 7.2)
5.0	26 Nov 19	• Change of TM • Section 7.2, table 1 – modification of legend point 2, clarified that assessment results can be taken from medical records • Section 7.2, table 2 – clarification the table is BNF guidelines only and sites will use localised prescribing guidelines.

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CLINICAL INVESTIATION PLAN APPROVAL

Pneumonia Investigation Bundle to Guide Therapy for Hospitalised Community Acquired Pneumonia (PIB CAP Study).

Signatures

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Moira Ross Trial Manager	Signature	Date
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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
ADE	Adverse Device Effect
AE	Adverse Event
CAP	Community Acquired Pneumonia
CEA	Cost Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
CIMD	Clinical Investigation of Medical Device
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRP	C reactive protein;
CTIMP	Clinical Trial of an Investigational Medicinal Product
CUA	Cost Utility Analysis
CURB65	Confusion status, urea level, respiratory rate, blood pressure, and age
DDD	Defined Daily Dose
DOOR	Desirability Of Outcome Ranking
ECTU	Edinburgh Clinical Trials Unit
FBC	Full Blood Count
GCP	Good Clinical Practice
ICER	Incremental Cost-Effectiveness Ratios (ICER)
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
IVD	*In Vitro* Diagnostic Medical Device
LFT	Liver Function Test
mRT-PCR	Multiplex Real Time Polymerase Chain Reaction
NEWS	National Early Warning Score

PI	Principal Investigator
PIB	Pneumonia Investigation Bundle
PROBE	Prospective Randomised Open Blinded Evaluation
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Service
QA	Quality Assurance
QALY	Quality Adjusted Life Year
RADAR	Response Adjusted for Duration of Antibiotic Risk
RCT	Randomised Controlled Triall
REC	Research Ethics Committee
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee
U-E	Urea and Electrolytes
USADE	Unanticipated Serious Adverse Device Effect

SCIENTIFIC SUMMARY

Design: Pragmatic, multicentre, open randomised controlled trial

Setting: 5 UK hospitals.

Target population:

- Inclusion criteria: patients ≥16 years old hospitalised with uncomplicated community acquired pneumonia (CAP)+CURB65 score ≥2.
- Exclusion criteria: No capacity to consent; active malignancy; immunodeficiency; solid organ transplant;pulmonary fibrosis; COPD on domiciliary oxygen therapy; mechanical ventilation; end of life care.

Health technology being assessed: utility of a pneumonia investigation bundle using fast multiplex real-time Polymerase Chain Reaction assays for 26 respiratory bacteria and viruses along with urine for Legionella Antigen test (using BinaxNOW®) to personalise antibiotic treatment. This bundle is being called “PIB CAP”.

Control treatment: investigations and treatment per NICE Pneumonia guideline.

Planned interventions: Half of the 843 participants will be randomised to management as per the NICE Pneumonia guideline and half with personalised treatment following PIB CAP investigations (admission throat swab, spontaneous sputum if available and urine for Legionella Antigen test). The group undergoing PIB CAP investigations will have standard antibiotic treatment as per NICE Pneumonia guideline, but will be personalised following PIB CAP results.

Assessments: Baseline, Days 7 (safety assessment) and 30 (assess recovery) and 1 year for health economic analysis. Interventions will be delivered by the clinical care team supported by the research nurse.

Timetable: 4 months for site training and to finalise approvals; 6 months pilot study; 35 months conducting the study; 6 months data analysis, writing the publication and reports; 1 month close of study and archiving.

Planned recruitment: 5 per calendar month per site.

Primary outcome: Desirability of Outcome Ranking (DOOR) to assess the efficacy and safety of PIB CAP therapy based on assessing (A) day 30 clinical response and (B) day 30 total antibiotics Defined Daily Dose (DDD) to ensure by narrowing antibiotics this does not lead to subsequent additional antibiotic use. What is the probability that a randomly selected participant will have a better DOOR if assigned to receive PIB CAP compared to standard treatment?

Statistical Rationale and Power calculation: A sample size of 358 in each group will have 90% power to detect a probability of 0.570 that an observation in the PIB CAP group is more than an observation in the standard care group using a Wilcoxon (Mann-Whitney) rank-sum test with a 5% two-sided significance level. To allow for potential dropouts this sample size will be increased to 400 per group [i.e. a 10% drop out rate].To incorporate a design with 4 equally spaced scheduled interim analyses increases the sample size to 843.

Health economics: A cost-utility (CUA) evaluation using standard NICE reference case specifications. Cost-effectiveness analysis (CEA) of cost per DDD reduction (exposure to antibiotics). Both CUA and CEA will be assessed by 30 day within trial analysis and longer term economic modelling.

Expertise in team: The team has expertise in pneumonia, microbiology, virology, statistics, health economics and trial methodology with full support from our experienced CTU.

PLAIN ENGLISH SUMMARY

There is an international drive to simplify antibiotic treatments to stop side effects from antibiotics and to stop the development of superbugs.

Pneumonia is an infection of the lung affecting 5 to 11 people out of 1,000 in the population. About 9% of patients admitted to hospital with pneumonia will die. Prompt and appropriate antibiotic treatment is needed to cure the pneumonia. International guidelines suggest using a combination antibiotic treatment for 7 to 10 days for patients admitted with pneumonia. However it is not completely known what antibiotics to prescribe or for how long antibiotic treatment is needed.

By the time patients are admitted to hospital with pneumonia many of them will already have had antibiotic therapy by their GPs. This can limit the results from standard pneumonia investigations. Tests currently used in the NHS can identify the cause of pneumonia in only 39% of patients. In addition, traditional methods to investigate pneumonia in the NHS take too long to give an answer. In many cases clinicians do not have enough information to confidently shorten or reduce antibiotic treatments.

We have developed a molecular test that identifies the cause of pneumonia in 87% of patients. Our test still works even if the patient has already started antibiotic treatment. Our test is very quick and we can have a result within a few hours. We call our test a "PIB CAP bundle".

Our virology team will set up this modern test in five major centres in the UK (Edinburgh, Newcastle, Nottingham, Southampton and London). The Edinburgh centre will check a sample of tests from other centres to ensure quality control.

We will invite patients who have been admitted to hospital with pneumonia to enrol onto our study. We will use a computer program to randomly decide which test participants will have. Half the participants will have the usual NHS tests and will receive the normal treatment for pneumonia. The other half of participants will have our molecular test and the results will customise their antibiotic treatment. We estimate that we will need to enrol 843 participants to the study in order to detect any differences between the group receiving standard NHS treatment and the group receiving customised antibiotic treatment.

The main aim of the study is to determine if the PIB CAP test can reduce the amount of antibiotics prescribed without any undesirable clinical side effects. We will count up how much antibiotic treatment each participant had, including any additional antibiotics that might have been needed after initial treatment. After 30 days each participant will have medical examinations and tests to see if it is safe to treat pneumonia with less antibiotics. We will also calculate if personalised antibiotic therapy is cost-effective for the NHS compared to the current treatment.

We will present the study results at local, national and international meetings and publish them in an open access medical journal. Results will also be made available to the public on the study website and from the British Lung Foundation.

1 INTRODUCTION

1.1 BACKGROUND

What is the problem being addressed?

There has been an international drive towards simplifying and reducing antibiotic prescribing due to the rising emergence of hospital acquired infections, side effects (in particular *Clostridium difficile* infection), and increased antimicrobial resistance.[1 2]

Community Acquired Pneumonia (CAP) is an excellent target group. CAP is the most common infectious disease requiring hospitalisation in western countries. It occurs in 5-11 per 1,000 population, and of these between 22-42% of adults are admitted to hospital and the in-patient mortality is around 5-14%.[3 4]

CAP can be caused by a wide range of microorganisms, necessitating broad-spectrum antibiotic treatment. To date clinicians have not had the confidence to narrow the spectrum of antibiotics in patients admitted with CAP due to the low yield from standard microbiological investigations and the time for results to be available. We have developed a pneumonia investigation bundle (PIB) that we believe can personalise treatment and overall effectively narrow the spectrum of antibiotics used for CAP without adversely affecting outcome.[5 6] This pneumonia investigation bundle (PIB CAP) uses fast multiplex real-time PCR (mRT-PCR) assays for 24 respiratory bacteria and viruses that captures most of the aetiological agents in CAP and provides results within 6 hours (compared to days to weeks from previous technologies).[5 7]

Our pilot work revealed pathogen detection in 87% of cases compared to 39% with culture-based methods. Molecular testing has the potential to enable de-escalation of antimicrobials in 77% of patients. [5]

This current study aims to have a microbiology aetiology result using PIB CAP within 36 hours of hospital admission and then give personalised targeted antibiotic treatment to safely reduce the total antibiotic burden. Although the technology can get a result within 6 hours, due to standard working hours for microbiology and virology staff, allowing the result of the PIB CAP to be delivered up to 36 hours after the test is administered is more pragmatic and more relevant for future NHS implementation.

We have done a literature review using MEDLINE, Cochrane and Clinicaltrials.gov website. A Cochrane review in 2012 concluded no benefit of survival or clinical efficacy with antibiotic coverage for atypical bacteria in patients hospitalised with CAP.[8] A systematic review and meta-analysis in 2014 found macrolide use was associated with lower mortality compared with non-macrolides in critically ill patients with CAP.[9] A further systematic review and meta-analysis in 2014 found that dual therapy reduced mortality but this was based on prospective and retrospective observational studies and the authors concluded that randomised controlled trials (RCT) are needed. [10]

A further systematic review in 2016 concluded for adults hospitalized with CAP, antibiotic therapy consisting of ß-lactam plus macrolide combination therapy or fluoroquinolone monotherapy initiated within 4 to 8 hours of hospital arrival was associated with lower short-term mortality (adjusted for possible confounders), supported predominantly by low-quality observational studies.[11]

There have been two major randomised controlled trials that have compared beta lactam monotherapy compared with beta lactam and macrolide combination therapy in moderately severe CAP. The first study in 580 patients compared the two above strategies and the primary outcome was clinical stability by day 7.[12] The study failed to show non-inferiority of beta lactam monotherapy with patients hospitalised with moderately severe CAP. They did show patients did less well with monotherapy with increased 30-day readmissions. They also did less well in the subgroup of patients with atypical or more advanced pneumonia from pneumonia scoring systems. The second study in 2,283 patients compared the two above strategies but also fluoroquinolone monotherapy and the primary outcome was 90-day mortality.[13] Their

study found non-inferiority with beta lactam monotherapy in patients admitted with pneumonia, other than critical care settings.

Current standard care pathway: Recommendation from NICE in their 2014 CAP guideline is for amoxicillin and macrolide for moderate severity pneumonia (Confusion status, urea level, respiratory rate, blood pressure, and age (CURB65) score 2) and combination therapy of a beta-lactamase stable beta-lactam (such as co-amoxiclav, ceftriaxone, cefuroxime, piperacillin with tazobactam) and a macrolide for severe pneumonia with a CURB65 score of three or more.[4] The addition of macrolides in moderate and severe pneumonia is recommended to cover the 'atypical pathogens' such as *Legionella species*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci* and *Coxiella burnetii*.

There has been increasing concern about the use of macrolides. In a 2012 observational study involving Tennessee Medicaid patients, the authors found that azithromycin use in comparison to amoxicillin had increased all cause and cardiovascular deaths in the 5 days of treatment, with the highest risk in patients with highest risk of cardiovascular disease.[14] A study found that patients that received clarithromycin for CAP exacerbations in hospital had increased cardiovascular events but no effect mortality at 1 year.[15] The widespread use of macrolides is also associated with increased macrolide resistance in *S. pneumoniae*.[16]

The British Thoracic Society (BTS) 2009 Community Acquired Pneumonia guideline recommend narrowing the spectrum of antibiotics when a pathogen is isolated but no such advice is given in the recent NICE Pneumonia guideline.[3 4] Our clinical experience is that in clinical practice narrowing the spectrum of antibiotics is rarely achieved, confounded by standard microbiology investigations identifying an aetiology of pneumonia in only about 30-40% of cases and the delay in standard care for microbial investigation results to be available, which hampers clinician confidence in narrowing the spectrum of antibiotics. Our pneumonia investigation bundle, however, identifies a pathogen in most cases (87%)[5] in a timely fashion and we believe will allow clinicians to safely personalise and narrow the spectrum of antibiotic therapy used. The NICE Pneumonia guideline recommends broad based therapy for hospitalised moderate and severe pneumonia in view of the high mortality in this group of patients. The research articles including systematic reviews and meta-analyses do not give us confidence that using narrow spectrum antibiotics is as safe as broad based therapy in patients with CAP admitted to hospital.

This proposed study is different from others in that we will personalise therapy based on the aetiological agent identified using our pneumonia investigation bundle. In our opinion this is a much more effective way to treat CAP and also will allow narrowing of the spectrum of antibiotic used without any deleterious effect or indeed escalate treatment if needed. This study is needed to check if this strategy works in a clinical setting across geographically disparate parts of the UK.

Planned care pathway: We believe an improvement to using standardised broad based antibiotic treatment for all CAP in the NHS would be to personalise treatment based on the microbiological aetiology of the CAP so that appropriate targeted antibiotic therapy is given. Using molecular testing, this current study aims to have a result within 36 hours and then give personalised targeted antibiotic treatment, thereby reducing the total antimicrobial burden needed to treat patients with CAP.

1.2 RATIONALE AND JUSTIFICATION FOR STUDY

As a result of an increase in hospital acquired infections there is a need to reduce antibiotic prescribing. To date clinicians have not had the confidence to narrow the spectrum of antibiotics in patients admitted with CAP and key barriers are the low yield from standard care investigations and the time for results to be available.

We have developed a pneumonia investigation bundle and we believe that personalised treatment will effectively narrow the spectrum of antibiotics recommended by national guidelines without adversely affecting outcome.[5 7] This pneumonia investigation bundle (PIB CAP) is using fast mRT-PCR assays for 24 respiratory bacteria and viruses and captures most of the aetiological agents in CAP and results available within 6 hours compared with days to

weeks from previous technologies.[5 6] Our pilot work revealed pathogen detection in 87% compared to 39% with culture-based methods. Molecular testing had the potential to enable de-escalation of antimicrobials in 77%.[5]

1.3 INTENDED PURPOSE OF INVESTIGATIONAL DEVICE

The PIBCAP assay is intended to diagnose more rapidly the aetiological agents in CAP. This current study aims to have a result within 36 hours of hospital admission. Then using the results of the PIBCAP assay to give personalised targeted antibiotic treatment safely reducing the antibiotic burden or giving the appropriate antibiotic based on the pathogen identified.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective is to explore whether participants admitted with community acquired pneumonia can safely receive personalised antibiotic therapy within 36 hours of hospital admission.

2.1.2 Secondary Objectives

Perform a health economic assessment and assess a number of key secondary endpoints.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Assess the probability that a randomly selected participant will have a better Desirability of Outcome Ranking (DOOR) if assigned to receive PIB CAP compared to standard treatment. In addition, we propose using the Response Adjusted for Duration of Antibiotic Risk (RADAR) to further subdivide (rank) within each level of the clinical outcome based on benefits and harms of PIB CAP therapy and ranking participants with respect to DOOR.[17 18] This is based on assessing:

(A) day 30 clinical response
and
(B) day 30 total antibiotics Defined Daily Dose (DDD)[19] to ensure by narrowing antibiotics this does not lead to subsequent increased antibiotic use.

A is ranked higher than B, i.e. the clinical response takes priority over DDD.

Clinical outcome (A) has 5 mutually exclusive hierarchical levels in descending order of desirability:

- Clinical recovery by day 30 without major adverse event/s
- Clinical recovery by day 30 with major adverse event/s
- Day 30 survival without clinical recovery but no major adverse event/s
- Day 30 survival without clinical recovery and with major adverse event/s
- Death by day 30

To make this a Prospective Randomised Open Blinded Evaluation (PROBE) Study an adjudication committee blinded to randomisation will evaluate both clinical recovery and major adverse events. The committee will comprise three Respiratory Principal Investigators (PI) or co-PIs. We are defining clinical recovery as resolution or improvement of symptoms and clinical signs related to CAP and a plasma C Reactive Protein (CRP) level of <20mg/L, and not on antibiotics related to CAP.

2.2.2 Secondary Endpoints

- CAP resolution at days 7 and 30 (Y/N)
- Major adverse events (Y/N) and number. Major adverse events = complicated parapneumonic effusion, empyema, lung abscess, vascular event (acute coronary syndrome or cerebrovascular accident) or antibiotic associated *C. difficile*, need for inotropic support, non-invasive or invasive ventilation or another major adverse event reported by the clinician and confirmed by the adjudication committee.
- Readmissions to hospital within 30 days due to CAP
- Death (at 30 days and time to death)
- Narrowing spectrum of antibiotics
- Macrolide DDD
- Alteration or addition of antibiotic therapy
- Length of hospital stay
- Antibiotic side effects
- Antibiotic costs
- Participant symptoms assessed using a pneumonia specific questionnaire [20]
- Antibiotic resistance in bacteria isolated
- Assess the optimum specimen(s) for assessment of CAP for bacteria, atypical bacteria and viruses
- Cost per Quality Adjusted Life Year at 30 days
- Cost per DDD of antibiotics at 30 days

Additional secondary endpoints will be analysed in the PIB CAP group

- Time to PIB
- To determine if clinicians personalise antibiotics based within 36 hours of hospital admission using the PIB CAP bundle CAP results
- Proportion of PIB CAP that produces a result

3 STUDY DESIGN

PIBCAP is a multicentre PROBE design RCT set in major UK hospital sites. Following recruitment to either PIBCAP or routine care participants will be monitored for 30 days.

The pneumonia investigation bundle will analyse respiratory tract samples for 24 pathogens using quantification and mRT-PCR. The pathogens included in the PIB CAP test are: *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii* and influenza A virus, influenza B virus, respiratory syncytial virus A&B, adenovirus, rhinovirus, human metapneumovirus, human coronaviruses (4 strains), *Mycoplasma pneumoniae*, *Legionella pneumoniae*, *Legionella* species, *Chlamydophil*a species and *Coxiella burnetii*. This assay utilises quantification as well as real-time PCR which enables rapid testing which generates clinically relevant results.

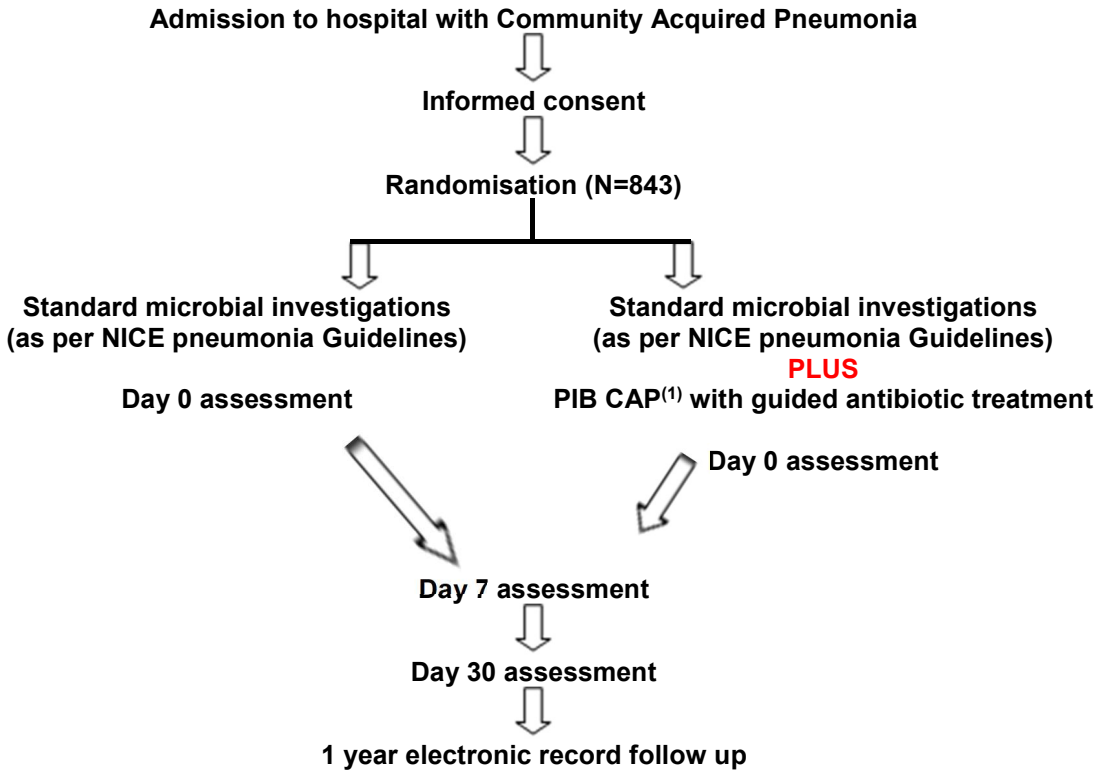

Figure 1: Study Design
(1) PIBCAP will be done using an admission throat swab & sputum (if available) and a urine sample for Legionella antigen test

The pneumonia investigation bundle consists of a number of mRT-PCR assays, including targets for internal and sample controls for quality control purposes and a range of bacterial and viral pathogens. These have been developed in the Medical Microbiology laboratory at the Royal Infirmary of Edinburgh by co-investigators Drs Templeton and Gadsby. This laboratory will act as the central laboratory to set up and distribute test reagents, provide training and supply quality control material to the other centres carrying out the PIB CAP assays.

The central laboratory will receive and archive specimen extracts from all centres at the end of the study period in order to carry out retrospective molecular testing for antibiotic resistance for epidemiological purposes. Specimens positive for *S. aureus* by PCR will be tested for the presence of MRSA, those positive for *S. pneumoniae* will be tested for penicillin susceptibility and macrolide resistance, and those positive for *H. influenzae* will be tested for the presence of beta-lactamase genes that confer amoxicillin resistance.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

843 participants will be recruited across at least five UK sites and allocated to one of two arms: management as per NICE pneumonia guidelines or to personalised treatment following PIB CAP investigations. Participants will be randomised 1:1 using a minimisation algorithm with minimisation factors of centre and CURB65 (2 or >2) and also a random element set at 20%.

4.2 INCLUSION CRITERIA

- Aged 16 and over
- Uncomplicated CAP confirmed by physician
- Hospitalised for CAP
- CURB65 score two or more

4.3 EXCLUSION CRITERIA

- No capacity to consent
- Active malignancy
- Immunodeficiency - defined as being on long term (>28 days) oral prednisolone 10mg or more per day or other long term disease modifying drug
- Solid organ transplant
- All forms of pulmonary fibrosis including usual interstitial pneumonia, asbestosis, non-specific interstitial pneumonia, hypersensitivity pneumonitis, active sarcoidosis
- Palliative treatment only
- COPD on domiciliary oxygen therapy
- Mechanical ventilation
- End of life care
- Previously randomised into this trial
- Participation in another CTIMP or CIMD interventional study

4.4 CO-ENROLMENT

Participants will not be permitted to participate in any other interventional clinical trials [i.e. Clinical Trial of an Investigational Medicinal Product (CTIMP) or a Clinical Investigation of Medical Device (CIMD)] while enrolled on the PIBCAP study. Participants will be permitted to take part in non-interventional research (e.g. questionnaire/tissue only studies) as per ACCORD Co-enrolment Policy (POL008 Co-enrolment) without formal documentation or authorisation from the Sponsor.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be identified by the clinical care team by assessing those admitted with community acquired pneumonia admitted via the front door (A+E, combined assessment unit/medical assessment unit, the wards or the high dependency unit). The research nurse is a member of the clinical care team.

5.2 CONSENTING PARTICIPANTS

Informed consent will be obtained by the PI or delegate. Research nurses may be delegated to obtain informed consent. Due to the nature of the study having to recruit participants and provide personalised antibiotic therapy within 36 hours of hospital admission using PIB CAP, participants will have a maximum of 30 hours to consider the information sheet before consenting.

5.3 SCREENING FOR ELIGIBILITY

The investigator or delegate will confirm the participant meets all the inclusion and exclusion criteria before randomisation.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Participants who have provided informed consent but are not subsequently randomised to the study will be considered screen fails. All screen fails will be captured in the electronic Case Report Form (eCRF).

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Eligible participants will be randomised using a web-based randomisation service hosted by the Edinburgh Clinical Trials Unit (ECTU) to avoid bias. Participants will be randomised 1:1 using a minimisation algorithm with minimisation factors of centre and CURB65 (2 or >2) and also a random element set at 20%. Communication of randomisation to the clinical trial team will be web-based.

5.5.2 Treatment Allocation

Following randomisation, both the participant and the Investigator will be notified of the assigned treatment allocation. Participants randomised to the PIBCAP arm will have their antibiotic therapy customised according to the results of the PIBCAP assay.

5.5.3 Emergency Unblinding Procedures

The study is unblinded.

5.5.4 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form (CRF), if possible. The participant will have the option of withdrawal from:-

(i) all aspects of the trial but continued use of data collected up to that point and allowing us access to medical records for electronic follow up (no further participant contact)
(ii) all aspects of the trial but continued use of data collected up to that point and not allowing us access to medical records for electronic follow up

Patients with no capacity to consent are excluded from the study. However is a participant loses capacity during the study they will not be withdrawn from the study or from their allocated treatment. The participant will continue to be treated and the study data will be collected.

6 IN VITRO DIAGNOSTIC DEVICE

6.1 STUDY DEVICE

6.1.1 Study Device Identification

Name of the investigational Device:	PIB CAP – a pneumonia investigation bundle using fast mRT-PCR for 24 respiratory bacteria and viruses.
Number of investigational devices:	1 (the same diagnostic kit will be used for all participants randomised to the PIB CAP arm)
Number of sites:	5

6.1.2 Study Device Manufacturer

NHS Lothian is the device manufacturer. The device was designed by:

Dr Kate Templeton
Medical Microbiology
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh
EH16 4SA

6.1.3 Study Device Information

PIB CAP is a non-CE marked *in vitro* diagnostic medical device (IVD) that detects a range of bacterial and viral pathogens by a number of mRT-PCRs assays. The study is intended to determine whether the IVD test results can help personalise antibiotic treatment. This study randomly allocates subjects to standard treatment only or standard treatment followed by personalised treatment.

The assay was developed by Drs Templeton and Gadsby, Medical Microbiology laboratory at the Royal Infirmary of Edinburgh.[5 6] All the PIB CAP test reagents will be set up and distributed from this central lab. Reagents for molecular assays will be made up in batches and supplied freeze-dried ready-aliquoted into consumables for use in the receiving laboratories. This will enable standardisation across all centres and minimal hands-on time and expertise required for the daily running of the assays.

QC, or pre-testing, of batches will be performed at the RIE lab. The validation procedure is outlined in the lab SOP and will be in accordance with ISO18159. The specificity of batches will be tested locally at each site using a validation panel to ensure compatibility. Batch release will be confirmed and documented by the RIE lab.
Transport, storage and release of the batches will be performed according to the PIB CAP shipping and distribution SOP. The sites will confirm receipt of specific batches. Batches that have passed their expiration date or are unused at the end of the study will be disposed of by the site according to local lab procedures.

Staff from the central lab will provide training to the other centres carrying out the PIB CAP assays. Only site staff trained in the PIBCAP SOP will perform the assay. As well as providing initial training in the use of the assays, the central laboratory will provide on-going technical support and will supply and analyse quality control material on a regular basis to ensure all centres are achieving expected results consistently during the study period. Throughout the study the Edinburgh central lab will check samples of tests from the labs at the other sites to ensure quality control. The QC (batch testing) will be done at the start and then again at 6 months if there has been no change in batch/lot number of reagents. If there has been a change of lot/batch number then the QC will be done. QA will occur at the start of the study and will be performed annually thereafter.

The instructions for use and storage, along with details of the manufacture of the IVD are included in the Investigator Brochure.

All analysis at the central lab will be conducted by NHS microbiology staff. The location of the central lab is

Medical Microbiology
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh
EH16 4SA

7 STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

The assessments performed at the day 7 visit are the safety assessments carried out as part of standard clinical care. These assessments will record these in the eCRF.

7.2 STUDY ASSESSMENTS

PIB CAP investigations will be performed on the samples (throat swab, spontaneous sputum if available and urine for Legionella Antigen test) taken at admission.

National Early Warning Score (NEWS) is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice, when patients present to, or are being monitored in hospital. Six simple physiological parameters form the basis of the scoring system.

CURB65 is a Pneumonia Scoring System (Score ranging 0-5).[1 2] A score of 2 or more is recommended to be managed in hospital. One point is attributed to each of the following:

A] New Onset Confusion, Mental test score 8 or less;
B] Blood Urea >7 mmol/L (> 19 mg/dL)
C] Respiratory Rate ≥30
D] Systolic Blood Pressure <90 mmHg or Diastolic Blood Pressure ≤60 mmHg
E] Age ≥ 65 years

	Baseline	Day 7 (+/- 1 day)	Day 30 (+/- 3 days)	1 year (+/- 1 month)
Baseline assessment(1)	√			
Clinical assessment(2)		√	√	
NEWS assessment(3)	√	√	√	
Health Care Utilisation questions(8)	√		√	
Pneumonia questionnaire(4)	√		√	
EQ-5D-5L questionnaire(4)	√	√	√	
FBC, U+E, LFT, CRP(5)	√	√	√	
CURB65 Score	√			
Chest X-ray	√			
Active arm(6) or Standard arm Intervention(7)	√			
Antibiotic type and usage		√	√	
Adverse events record	√	√	√	
Health economics follow up(9)				√

Table 1: Study assessments

(1) Includes consent, medical history, concomitant medication, prior antibiotic treatment, chest examination.

(2) Includes clinical examination, if required.

(3) National Early Warning Score (NEWS2) measure respiratory rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, and temperature.

(4) If questionnaires cannot be completed during the assessment they are to be completed as soon as possible afterwards. The date of completion of questionnaires is to be recorded in the CRF.

(5) Full Blood Count (FBC), Urea and Electrolytes (U+E), Liver Function Test (LFT), C-reactive protein (CRP)

(6) Active arm: PIBCAP: throat swab + sputum (if available) taken for mRT-PCR and urine sample (if available) taken for Legionella Antigen test (using BinaxNOW®))

(7) Standard arm: investigations as per NICE Pneumonia Guideline. [4]

(8) Includes use of primary care services, NHS phone help lines, outpatients, A&E, ambulance services, hospital admissions and antibiotic use.

(9) Hospital admissions only. Follow up is done through patient medical records only, no participant contact is required.

Some study assessment results may be obtained from participants' medical records.

Standard Treatment Based on CURB65	**Standard Care**	**Duration**[1]
CURB65 2	Amoxicillin + Clarithromycin	7 days
CURB65 ≥3	Co-amoxiclav + Clarithromycin	7 days
Atypical pathogen	Clarithromycin (levofloxacin if *Legionella* suspected or confirmed)	14 days
Influenza A or B	Oseltamavir + Co-amoxiclav	Oseltamavir (5 days) Co-amoxiclav (7 days)
Other Viral pathogen	Co-amoxiclav	7 days
mRT-PCR Directed Treatment Based on Pathogen	**PIB CAP Care**	**Duration**
Streptococcus pneumoniae	Amoxicillin	7 days
Haemophilus influenzae or *Moraxella catarrhalis*	Doxycycline[2]	7 days
Staphylococcus aureus	Flucloxacillin	7 days
Escherichia coli or *Klebsiella pneumoniae*	Co-amoxiclav	7 days
Pseudomonas aeruginosa or *Acinetobacter baumannii*	Ciprofloxacin	7 days
Atypical pathogen	Clarithromycin (levofloxacin if *Legionella* suspected or confirmed)	14 days
Influenza A or B	Oseltamavir + Co-amoxiclav	Oseltamavir (5 days) Co-amoxiclav (7 days)
Other Viral pathogen	Co-amoxiclav	7 days
No pathogen identified	Co-amoxiclav	7 days

Table 2: Study Treatments

Antibiotic class, duration and doses as per BNF. The use of intravenous antibiotics will be in accordance with NICE Pneumonia Guideline.[4] If >1 pathogen is identified, the appropriate treatment will be used to cover the pathogens. Treatment can be altered if there is a complication or clinical concern in either group.

[1] The recommended duration from NICE guidelines. The actual duration will be recorded in the CRF.

[2] Doxycycline can be substituted in penicillin allergic participants.

Table 2 is to be used for guidance only. Sites will follow local practice in relation to antibiotic prescribing for standard care. Participants randomised to PIBCAP will receive a targeted antibiotic regimen.

7.3 LONG TERM FOLLOW UP ASSESSMENTS

Central NHS records and GP records will be used to electronically assess health care utilisation at 12 months.

7.4 STORAGE AND ANALYSIS OF SAMPLES

The viral throat swab, sputum samples and urine samples obtained from participants assigned to the PIB CAP treatment arm will be batched and sent from all centres to the -70°C storage freezers (PI Prof A Hill), room C2.25, Queen's Medical Research Institute, University of Edinburgh for storage in the -70°C freezer after PIB CAP analysis in each of the study centres. These samples are being analysed for resistance to antibiotics. We will obtain consent for long term storage of the samples for future research.

8 DATA COLLECTION

8.1 Source Data Documentation

Data recorded by designated trial staff on the trial specific eCRF will be obtained from the source documents, these include the medical notes, lab results, medical images and paper questionnaires completed by the subjects. Trial specific paperwork completed during the trial will form Source Data and be kept at site. Source documents are those in which information is recorded and documented for the first time.

The questionnaires will be filled in by the participants at the time of the assessments. For participants who are otherwise too unwell to complete the survey, an appropriate surrogate (such as a close family member) will be asked to complete the form on their behalf in line with NICE reference case guidance.

8.2 Case Report Forms

CRFs will be completed by the research nurse (or delegate). Table 1 details what data are collected at baseline, Day 7 and Day 30. At the 12 month follow up the investigator, or delegate, will collect data on any hospital admissions since the participant's study visit at Day 30. Hospital admission data will be entered into the eCRF. The Edinburgh Clinical Trials Unit (ECTU) will design the eCRF.

9 DATA MANAGEMENT

9.1 Personal Data

The following personal data will be collected as part of the research:

- Initials, date of birth

Personal data will be collected and stored by the research team at the site. The clinical care team and study data managers will have access.

Paper documentation containing personal data will be stored in a locked cabinet or room within a secure area (i.e. accessible only by authorised staff). Personal data stored electronically will only be accessible by authorised members of the study/clinical care team. A unique login name and password will be required to access electronic personal data. The electronic data are held on a secure ECTU server.

Personal data will be stored for 3 years. The sponsor will be contacted before paper documentation is destroyed.

9.1.1 Transfer of Data

All data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

9.1.2 Data Processor

The data processor is the CI, Prof Adam Hill.

The data processor is a natural or legal person, public authority, agency or other body which processes personal data on behalf of the controller

9.1.3 Data Controller

The data controller is the study sponsor ACCORD.

The data controller is the organisation who determines the purposes for which, and the manner in which, any personal data are processed.

10 STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

A sample size of 358 in each group will have 90% power to detect a probability of 0.570 that an observation in the PIB CAP group is more than an observation in the standard care group using a Wilcoxon (Mann-Whitney) rank-sum test with a 5% two-sided significance level. To allow for potential dropouts this sample size will be increased to 400 per group (i.e. a 10% drop out rate). We anticipate the dropout rate will be very low in this study of short duration with minimal participant intervention. To incorporate a group sequential design using a Lan-DeMets alpha spending rule with Fleming O'Brien boundaries with 4 equally spaced scheduled interim analyses increases the sample size to 843.

10.2 PROPOSED ANALYSES

All statistical analyses will be governed by a comprehensive pre-specified Statistical Analysis Plan (SAP), to be authored by the study statistician and agreed by the Trial Steering Committee (TSC) and the Independent Data Monitoring Committee (DMC), who will have a separate SAP detailing the unblinded formal interim analyses under the group sequential design.

The primary outcome will be analysed using the Wilcoxon-Mann-Whitney rank sum test, under an intention to treat principle, as appropriate for a superiority design. We will also consider a potentially more powerful analysis using Koch's non-parametric ANCOVA[21] to adjust for pre-specified baseline covariates felt to be strongly related to outcome (for example, CURB65 score), and adjusting for centre as a random effect.

As a supporting analysis we will look at just the clinical outcome (without adjusting for the DDD via the RADAR approach) using an ordinal logistic mixed effects regression. We will explore the robustness of the findings to any missing data using multiple imputation according to Rubin's approach under an assumption of missing at random. We do not expect the level of missing data to be high, and hopefully less than the assumed 10%, making an approach assuming informative missing ness unlikely to be either necessary or feasible.

Secondary outcomes will be analysed using methods appropriate to their distribution. Mortality will be compared between randomised groups using logistic regression (at 30 days – Y/N) and time to death by Cox proportional hazards regression. The narrowing of the antibiotic spectrum will be compared between randomised groups according to the count of different antibiotics used (via a Poisson or Negative Binomial regression). Comparison between randomised groups for macrolide DDD will be using normal linear regression; likewise, hospital length of stay (with possible transformation of the outcome to address skewness). Participant symptom questionnaire will be analysed using either linear, logistic or ordinal regression depending on how the scores are categorised. Frequency of antibiotic side effects will be considered as either count or binomial data (Poisson / negative binomial or logistic regression).

Apart from the interim analyses under the group sequential design, the final analysis will be a single analysis at study end, and a level of significance of 0.05 will be used throughout, with no adjustment for multiple comparisons.

A health economic analysis will evaluate the cost-effectiveness of the PIB CAP intervention to usual care. To maximise UK policy relevance, the analysis will follow NICE reference case recommendations[22] including: adoption of an NHS and personal social service (PSS) costing perspective for primary analyses; cost-utility approach (CUA, results presented in terms of incremental cost per quality adjusted life year (QALY), with QALYs derived from EQ-5D-5L using a standard UK algorithm[23] via an area under the curve approach); discount rate of 3.5% for both costs and QALYs (where applicable); use of probabilistic sensitivity analysis; and, provision of value of information analysis to inform future research.

Of additional interest beyond the outcomes captured by CUA is reduction in exposure to antibiotic use as this can lead to the development of resistance. For this reason additional cost-effectiveness analyses (CEA) in the form of reductions in cost per antibiotic defined daily dose (DDD) per participant will also be presented.

For participants who are otherwise too unwell to complete the survey, an appropriate surrogate (such as a close family member) will be asked to complete the form on their behalf. Where this has been undertaken, a dummy variable denoting that this has occurred will be recorded to aid baseline co-variate adjustment if necessary.

Where possible, primary care (general practice and district nurse consultations and community prescribing) and secondary care (inpatient & outpatient admissions, A&E visits, ambulance trips) utilisation will be extracted from medical records. Participant consent will be obtained for electronic follow up of participants to assess rates of readmission and mortality beyond the observed 30-day trial period to assist with the modelling. Community prescribing, EQ-5D-5L and any primary and secondary care utilisation not extractable from records will be obtained by participant self-report at baseline and 30 day follow ups. Health care utilisation will be combined with standard UK price weights to estimate costs. Uncertainty will be assessed through probabilistic sensitivity analyses (PSA) with deterministic analysis around relevant methodological assumptions.

Within trial analysis will assess CUA and CEA over the 30 day observed period likely through the use of generalised linear models which are recommended in this area to account for skew.[24] Longer term impacts of the intervention will be assessed via economic modelling. This is expected to be most relevant to capture any differences in mortality between arms and as has been used in previous studies,[25] though other interactions may also be incorporated as required. Specifics of the model structure will be determined through consultations with clinical experts and targeted searches of the literature to populate model parameters not observable through the trial data to strike an appropriate balance of generalisability and pragmatism. It is anticipated that this will likely take the form of Markov chain modelling though alternatives will be explored. PSA will then be undertaken likely utilising a methods of moments approach and the desired incremental cost-effectiveness ratios (ICER) and cost-effectiveness acceptability curves (CEAC) generated.

Finally, the value of further research will be determined and compared using value of information analysis to identify the parameters which are most likely to change the decision recommended by the model such as: those with a high degree of uncertainty; high weighting; or, an important structural role in the model.

11 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. This task may be delegated to a qualified member(s) of the research team. Assessment of events may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting adverse events (AEs).

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop, up to the day 30 assessment. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the participant's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

11.1 DEFINITIONS

11.1.1 Adverse Event

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in a subject enrolled into a trial, including occurrences which are not necessarily caused or related to the investigational medical device.

11.1.2 Serious Adverse Event (SAE)

Adverse event that:

- results in death;
- is a life threatening* illness or injury;
- requires hospitalisation^ or prolongation of existing hospitalisation;
- Medical or surgical intervention required to prevent any of the above
- Leads to foetal distress, foetal death or consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the Investigator

A planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Investigation Plan (CIP), without a serious deterioration in health, is not considered to be a serious adverse event.

* Life-threatening in the definition of an SAE refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^ A hospitalization for pre-existing condition that was planned prior to randomisation, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

11.1.3 Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

An ADE includes any event that is a result of a use error or intentional misuse. Use error refers to an act or omission of an act that results in a different device response than intended by the manufacturer or expected by the user. An unexpected physiological response of the subject does not in itself constitute a use error.

For example, in this study an ADE would be if an error was made by the lab running the diagnostic assay, a member of the clinical care team then acted upon this erroneous information and a participant experienced an AE.

11.1.4 Serious Adverse Device Event (SADE)

A SADE is an adverse event effect that has resulted in any of the characteristics of a SAE (see section 11.1.2). This includes device deficiencies that might have led to a SAE if;

- Suitable action had not been taken
- Intervention had not been made
- If circumstances had been less fortunate

11.1.5 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the Investigator's Brochure (IB).

11.1.6 Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling. For example, in this study if the diagnostic PIBCAP assay failed to provide a result this would be a device deficiency.

11.2 IDENTIFYING AEs ADEs, SAEs AND SADEs

All AEs, ADEs, SAEs, SADEs and USADEs will be recorded in the participants medical records from the time a participant signs the consent form to take part in the study until the end of study assessments at day 30.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop.

Participants will be asked about the occurrence of AEs/SAEs and SAE/SADEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE and SAE/SADEs occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded in the medical records. AE/ADEs and SAE/SADEs may also be identified via information from support departments e.g. laboratories, device software. In the case of an AE/ADE, the Investigator should initiate the appropriate treatment according to their medical judgment.

11.3 RECORDING AEs ADEs, SAEs AND SADEs

When an AE/ADE/SAE/SADE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator or delegate will then record all relevant information in the SAE form (if the AE/ADE meets the criteria of serious). SAEs/SADES will be followed up until resolution or death of the clinical investigation participant. All AEs, ADEs, SAEs, SADEs and USADEs will be recorded in the participant's medical records. All AEs that are endpoints and all SAEs will also be recorded in the CRF..

Information to be collected includes type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

11.4 ASSESSMENT OF AEs ADEs, SAEs, SADEs and USADEs

Seriousness, causality, severity and expectedness will be assessed by the PI or another suitably qualified physician in the research team who has been delegated this role.

The CI may not downgrade an event that has been assessed by an Investigator as an SAE, SADE or USADE but can upgrade an AE to an SAE, SADE or USADE if appropriate.

11.4.1 Assessment of Seriousness

The Investigator or a delegated suitably qualified physicians in the research team will make an assessment of seriousness as defined in Section 11.1.2.

11.4.2 Assessment of Causality

The Investigator or a delegated suitably qualified physicians in the research team will also make an assessment of whether the AE/SAE is likely to be related to the device according to the following definitions:

- Unrelated: where an event is not considered to be related to the device.

- Possibly Related: The nature of the event, the underlying medical condition or temporal relationship make it possible that the ADE has a causal relationship to the device.

Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

11.4.3 Assessment of Expectedness

If an event is judged to be an ADE, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the investigator brochure. The event will be classed as either;

Expected: the ADE is consistent with the effects of the device listed in the investigator brochure.

Unexpected: the ADE is not consistent with the effects listed in the investigator brochure.

11.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/ADE/SAE/SADE and record this on the CRF or SAE/SADE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.5 REPORTING OF SAEs/SADEs/USADEs/Device Deficiencies

Once the Investigator becomes aware that an SAE, SADE or USADE, including device deficiencies, has occurred in a study participant, the information will be reported to ACCORD **within 24 hours** using Template report CR012-T01 SAE (Devices) Form or CR012-T02 Medical Device Deficiency Form where appropriate.

SADE and device deficiency reports must provide an assessment of causality at the time of initial reporting to ACCORD. Initial reports will be submitted within 24 hours of the investigator becoming aware of the event. If the Investigator does not have all information regarding an SAE, SADEs or device deficiencies, they should not wait for this additional information before notifying ACCORD. The SAE/SADE report form can be updated when the additional information is received. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

The SAE/SADE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 11.4.2, Assessment of Causality and 11.4.3, Assessment of Expectedness.

The SAE/SADE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to safety@accord.scot Only forms in a pdf format will be accepted by ACCORD via email. To ensure patient confidentiality, SAE, SADE and device deficiency reports will detail the trial participant number only.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF) and in the Trial Master File (TMF).

The following events are expected in this patient populations and will not be reported to the ACCORD office within 24 hours, even in situations where these expected events fulfil the criteria as serious (as defined above):

11.6 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for reporting any serious adverse event that is related and unexpected (USADE) to the REC. ACCORD has a legal responsibility to notify the relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SAEs and SADEs will be reported within 2 calendar days and all other SAEs and SADEs will be reported within 7 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of any other arising safety information.

ACCORD will also report SADEs/USADEs via the yellow card reporting system (https://yellowcard.mhra.gov.uk/) quoting the MHRA registration number for the study.

11.7 FOLLOW UP PROCEDURES

After initially recording an AE/ADE or recording and reporting an SAE/SADE, the Investigator will follow each participant until resolution or death of the participant. Follow up information on an SAE/SADE will be reported to the ACCORD office.

AEs/ADEs still present in participants at the last study visit will be monitored until resolution of the event or until no longer medically indicated.

There are no other requirements for subject follow up in regards to the study.

12 PREGNANCY

Pregnancy is not considered an AE or SAE; however, the Investigator will collect pregnancy information for any female participants or female partners of male participants who become pregnant while participating in the study. The Investigator will record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

Pregnancy isn't thought to be an issue in this study.

All pregnant female participants and partners of male participants will be followed up until following the outcome of the pregnancy.

13 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (CI and PI in Edinburgh), a Trial Manager and coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the CI. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

13.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the TSC, the draft template for reporting and the names and contact details are detailed in Appendix 2.

13.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the DMC and the names and contact details are detailed in Appendix 3.

13.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

13.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the Quality Assurance (QA) group, in accordance with ACCORD governance and sponsorship Standard Operating Procedures (SOPs). Input will be sought from the CI or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions (delete if no adaptations were possible) could be incorporated into to trial design.

13.6 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD QA Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

14 GOOD CLINICAL PRACTICE

14.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP). Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

14.2 REGULATORY COMPLIANCE

The study will be registered as an IVD for performance evaluation. A notification of intent to carry out a clinical investigation as well as an annex VIII statement according to the IVD Directive (98/79/EC) will be sent to the MHRA before commencement of the proposed investigation. A letter of no objection from the MHRA is not required.

14.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the clinical investigational plan and any clinical investigational plan amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also

the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

14.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any clinical investigational plan specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the ISF and participant's medical notes.

14.3.2 Study Site Staff

The Investigator must be familiar with the clinical investigational plan and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the clinical investigational plan and their trial related duties.

14.3.3 Data Recording

The PI is responsible for the quality of the data recorded in the CRF at each Investigator Site.

14.3.4 Investigator Documentation

The PI will ensure that the required documentation is available in local ISFs.

14.3.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

14.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information. Access to collated participant data will be restricted to those individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

15 STUDY CONDUCT RESPONSIBILITIES

The trial will be led by Adam Hill and coordinated by ECTU. The following oversight committees will be formed in line with sponsor SOPS where available

- Project Management Group
- Trial Steering Committee
- Independent Data Monitoring Committee
- Blinded adjudication committee

15.1 CLINICAL INVESTIGATIONAL PLAN AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the CI.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended clinical investigational plan.

15.2 MANAGEMENT OF CLINICAL INVESTIGATIONAL PLAN NON COMPLIANCE

Prospective clinical investigational plan deviations, i.e. clinical investigational plan waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent clinical investigational plan amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Clinical investigational plan deviations will be recorded in a clinical investigational plan deviation log for each site and logs will be submitted to the sponsors every 3 months, in accordance with ACCORD SOP CR010. Each clinical investigational plan violation will be reported to the sponsor within 3 days of becoming aware of the violation. All clinical investigational plan deviation logs and violation forms should be emailed to QA@accord.scot

15.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the CI, PI or delegates, the co-sponsors (QA@accord.scotmust be notified within 24 hours, in accordance with ACCORD SOP CR003.

It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

15.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the clinical investigational plan defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

Following publication of the primary paper, a de-identified individual participant data set will be submitted to data archiving for sharing purposes. Access to the de-identified dataset will be under a controlled access model in line with ECTU policies at that time.

15.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

15.6 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Clinical investigational plan has been designed by the CI and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor Clinical investigational plan design by the CI and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the UK NHS will have the benefit of NHS Indemnity.

16 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

16.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

16.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

All proposed publications and presentations must be discussed with the-CI and sent to ECTU prior to their release. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

The data will be disseminated (with the support of the British Lung Foundation) at local, national level via publication in peer review journals and at international meetings in Respiratory Medicine, Internal Medicine and Infectious Diseases. Results, links to study outputs and a general summary of the results will be available for the public on the PIB CAP page of the ECTU website (https://www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies).

16.3 PEER REVIEW

The funder study report will undergo independent peer review according to NIHR HTA procedures.

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Appendix 1: Initial feasibility and pilot study

The internal pilot provides clear progression criteria based on achieving milestones on (a) satisfactory processing of samples, (b) clinician adherence/fidelity with the antibiotic prescribing, (c) recruitment of participants, and (d) clinician acceptability of the intervention.

The proposed pilot takes place over 6 months, starting in project month 5, and involving all 5 study sites. Edinburgh will be recruited in the first month of the internal pilot, followed by Nottingham, Newcastle, Southampton, and London in internal pilot months 2, 3, 4 and 5, respectively. Assuming they come on-stream in the beginning of a month, that generates 6, 5, 4, 3, and 2 month's recruitment or 20 internal pilot centre months in total. There are then 35 additional months of recruitment at steady state, making 195 centre months in total. The maximum sample size required under the group sequential design is 843 participants, which equates to 843/195 = 4.5/centre/month. 20 centre months at 4.5/month gives an expected total of 90 randomised in the internal pilot. We will take a statistical approach to defining the 'Red-Amber-Green' stop-go criteria on patient recruitment. If the 5 sites are following independent identically distributed Poisson distributions this internal pilot total will approximately follow a normal distribution, with a mean of 90 and standard deviation of around 10. We will therefore continue (Green) if we are within 2 standard deviations of 90 i.e. 71 or more; we will modify (Amber – in this context, additional sites) if we are between 2 and 4 standard deviations (i.e. 51 to 70); and we will consider abandoning (Red) if we are at 50 or less recruits. We will discuss this decision process carefully with the HTA Board at the time. We think this progress criterion on recruitment is clear and robust since (a) it targets over 10% (90 of 843) of the maximum sample; (b) it is based on data from all 5 sites (so there should be no disconnect in scaling up as is often seen in pilots based on selected sites); (c) it assumes the required recruitment rate over the life of the study; and (d) it is based on objective statistical criteria.

In addition to this stop-go on recruitment we will, as stated, also require the sample processing at each site to be above an acceptable quality level, and that clinician adherence with study processes is acceptable (at least 60% clinician concordance) with: fidelity with NICE guidelines for both groups; antibiotics prescribed in keeping with PIB CAP results as per Table 1 reviewed by the adjudication committee. If clinician concordance is below this level, we will instigate professional training sessions for the clinicians to improve this and continue monitoring to ensure that the improvement is sustained. Validity testing of the multiplex PCR for respiratory pathogens has already been completed.[5 6]

We will also investigate clinicians' acceptability of the intervention during the internal pilot. The successful participation of the clinicians in the 5 sites will *de facto* provide evidence of their acceptance of the intervention (further informed by measuring their fidelity with the intervention) – but we think it would be useful to gauge the level of understanding & support the PIB CAP intervention has before the findings of this definitive trial are in. So, in the period of the internal pilot we will design and deploy a survey (using Survey Monkey) of clinicians via appropriate use of the e-mail lists from the Scottish Thoracic Society and British Thoracic Society to assess the clinicians' opinions and attitudes towards PIB CAP and issues around its adoption into practice if that became indicated.

If we are in the amber or the red zone after the internal pilot we will discuss carefully the problems with the sites and the iDMC and TSC, and hence progression with the HTA. We do not anticipate insurmountable problems with recruitment from our experience with other trials. Last year in Edinburgh and Nottingham there were around 1,200 patients admitted with CAP (personal communication). The patient groups involved with the project feel this is a study that patients with pneumonia will want to participate in, not only to help themselves but for the benefit of future patients as well.

Post pilot study

Assuming the pilot study is successful we will closely monitor recruitment rates throughout the study. If the recruitment rates are lower than expected, there are several centres willing to support recruitment as needed via the Respiratory NIHR portfolio. Recruitment rates are based on analysis of prior trials, and the entry criteria aligning to real life caseloads should facilitate recruitment. Again if clinician adherence is lower than 40%, we will have focus group meetings across all sites to improve this.

Planned recruitment:

5 per calendar month per site. We will recruit the 5 sites in a staggered way over the 6 months of the pilot / feasibility, and then continue with an additional maximum of 35 months of recruitment. Allowing for 11 effective full months per year (half months at Christmas and in the summer) we will have up to 195 centre months to recruit 843 participants. Under the group sequential design there are formal interim analyses at 25%, 50%, 75% and a final analysis at 100% (respectively 211, 422, 633 and 843 participants with mature data on the primary outcome at 30 days), with the possibility of stopping for overwhelming evidence of efficacy or futility at each of these interim analyses. The planned efficacy boundaries are Z-statistics of 4.33, 2.96, 2.36, and 1.96 (nominal P-values of <0.0001, 0.0015, 0.0092 and 0.0248) and the planned futility boundaries have Z-statistics of -1.43, 0.29, 1.25, and 1.96 (with nominal P-values of 0.077, 0.615, 0.894, and 0.975). It is possible to integrate the operating characteristics of these stopping rules at each interim analysis to calculate that if this experiment was run a large number of times, the expected sample size would be 540 participants – thus a considerable potential reduction over the unadjusted fixed sample size of 800 without the interim analyses under the group sequential design. If a decision to stop was indeed taken, it could be implemented probably before no more than an additional 50-75 participants were randomised.

Appendix 2: Trial Steering Committee

Responsibility for calling and organising the TSC meeting will lie with the CI Prof Adam Hill. At least one meeting will be conducted before recruitment begins. The terms of reference of the TSC and the list of TSC members are detailed in the PIBCAP TSC charter which is filed in the TMF.

Appendix 3: Data Monitoring Committee

The terms of reference of the DMC and the list of DMC members are detailed in the PIBCAP DMC charter which is filed in the TMF.